# Assignment of Three Patients with Xeroderma Pigmentosum to Complementation Group E and Their Characteristics

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Three cases belonging to xeroderma pigmentosum (XP) complementation group E were analyzed clinically and photobiologically. The three Japanese patients were a 50-yr-old female (XP80TO), a 42-yr-old female (XP81TO), and a 41-yr-old female (XP82TO). They were assigned to complementation group E by the cell hybridization study. All showed lowered minimal erythema doses between those of normal Japanese and XP group A subjects at wavelengths of 280, 290, and 300 nm of monochromatic ultraviolet (UV) light. Patients XP80TO and XP81TO, but not patient XP82TO, showed a delayed peak reaction at 48 h to UV erythema. All fibroblast strains from these patients had a reduced level of 40%–44% unscheduled DNA synthesis (UDS) after irradiation with 10 J/m$^2$ of 254 nm UV. Primary cultured epidermal cells from these patients exhibited a relatively low level of UDS (ie, 38%–51% of normal epiderma cells). All of the group E fibroblast strains were twice as sensitive to 254 nm UV killing [n (extrapolation number) = 1.3–1.8, Do (mean lethal dose) = 2.2–2.8 J/m$^2$)] as normal fibroblasts ($n = 1.5$, $Do = 5.0$ J/m$^2$). All of the above group E patients had mild XP symptoms, but not neurological abnormalities, at the fifth decade of age. Patients XP80TO and XP81TO had developed skin malignancies (patients XP80TO developed three basaliomas; patient XP81TO developed two basaliomas) at the ages of 46 and 41 yr, respectively. *J Invest Dermatol 90:152–157, 1988*

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by hypersensitivity of the skin to sunlight, a high frequency of cutaneous malignancies, and defective repair of ultraviolet (UV) —induced pyrimidine dimers in the DNA [1,2]. At present, XP comprises at least nine excision-defective complementation groups (A through I) and an excision-proficient variant form. In Japan, many patients with XP have been assigned to group A and variant [3], while groups C and D are more common in Europe and the United States. However, group E patients are still rare: only five cases in Europe [4–6] and three cases in Japan [7,8] have been reported so far.

Here we describe the additional assignments of three affected patients to group E on the basis of the heterodikaryon complementation test and their clinical characteristics. As cellular characteristics, we also report UV hypersensitivity and UDS level in these fibroblast strains. Besides, in XP it is important to investigate the relationship between skin carcinogenesis and DNA repair defects in epidermal cells. We have previously demonstrated that XP group A epidermal cells in culture show a severe defect of UDS comparable to the fibroblast level, while XP-variant epidermal cells have an appreciably lowered UDS, compared with 100% UDS in the fibroblasts [9]. For further information, extensive studies are needed in epidermal cells of various XP groups. Thus, we will examine the level of UV-induced UDS in the presently assigned group E epidermal cells and compare this level with that in their fibroblasts.

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Abbreviations:
MED: minimal erythema dose
UDS: unscheduled DNA synthesis
XP: xeroderma pigmentosum

## MATERIALS AND METHODS

**Cell Strains and Culture Conditions** We obtained small skin samples (about 2 × 2 mm) from the XP patients (the biopsy specimens were taken from uninvolved skin of the elbows). Fibroblast and epidermal cell cultures were prepared by the method described previously [9].

The reference fibroblast strains used for the complementation test were as follows: normal: NHSF6 (authors) [10,11]; complementation group A: XP6KO (authors) [7,10]; group C: XP40KO (authors) [7]; group D: XP59TO (authors) [13]; group E: XP24KO (authors) [7]; group F: XP25KO (authors) [14]; group G: XP2BI (from Dr. D. G. Harnden) [15]; group H: GM3248 (purchased from the Institute for Medical Research) [16]. Group B and I strains were not available. Cells were cultured in Eagle's minimum essential medium supplemented with 10% fetal calf serum (Hyclone) at 37°C in an atmosphere of 5% $CO_2$ in air.

**Photosensitivity Test of the Skin** Using a quartz prism monochromator and a 1-kW xenon arc source (described previously [17]), the minimal erythema dose (MED) of the patients are determined by exposing the unexposed skin of the back to monochromatic UV light at selected wavelengths of 280, 290, and 300 nm and by recording MEDs at 24, 48, and 72 h after irradiation.

**Clonogenic Ultraviolet Survival** Clonogenic UV survival

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curves of normal and XP cells were determined as described previously [10]. After attachment, cells were washed with phosphate-buffered saline, irradiated with 254 nm UV light, and incubated for 2 wk in order to determine clone survival. Survival-curve characteristics were defined by the parameters of extrapolation number ($n$) and mean lethal UV dose ($Do$).

**Complementation Analysis and Measurement of Unscheduled DNA Synthesis (UDS)** For the complementation group assignment, we employed our specific heterodikaryon method, which facilitates the easy identification of heterodikaryons and homodikaryons in fused populations by differential Latex bead labeling [7]. Briefly, the test and reference cells (see above) were labeled with large (1.09 $\mu$m) and small (0.48 $\mu$m) Latex beads (LB and SB) (Dow Chemical Co.), respectively, and then the dense cocultures were fused with 45% polyethylene glycol. Cells were replated sparsely on plastic cover-slips 2 h after fusion and incubated at 37°C for another 24 h prior to UV irradiation. The cells were then irradiated with 10 J/m$^2$ of 254-nm UV, and radio labeled with 10 $\mu$Ci/ml of [5-*methyl*-$^3$H]thymidine (sp act, 46 Ci/mmol; Amersham International, Bucks, U.K.) at 37°C for 3 h in the absence of hydroxyurea. Autoradiography was carried out by applying a Sakura NR-M2 emulsion (Konishiroku Photo Co., Tokyo, Japan) and by exposing for 7 days in the dark at 4°C. We counted the numbers of silver grains on 50 lightly labeled cells each of heterodikaryons (with both LB and SB), test-cell homodikaryons (LB only) and reference-cell homodikaryons (SB only). The average number of grains per single nucleus after subtraction of background was calculated as a measure for UDS. The UDS per nucleus in UV-irradiated homodikaryons was the same as that in the corresponding unfused monokaryons. As a result, comparison of UDS (as a percentage of normal-cell homodikaryon) between various heterodikaryons and homodikaryons was able to distinguish whether or not genetic complementation had occured.

**Ultraviolet-Induced Unscheduled DNA Synthesis in Primary Cultured Epidermal Cells** We also measured UDS in epidermal cells by the method described previously [9]. Small-skin samples obtained from patients and normal subjects were cut into 0.5–1.0-mm$^2$ pieces and cultured using the explant-outgrowth method in Eagle's minimum essential medium supplemented with 10% fetal calf serum. Ultraviolet-irradiation was carried out at doses of 5–20 J/m$^2$ between days 7 and 14 after cultivation when epidermal cell sheets of about 30 cell layers had been formed from explants. Ultraviolet-irradiated and unirradiated cells were incubated for 3 h in medium containing 5 $\mu$Ci/ml [*methyl*-$^3$H]thymidine (sp act, 25 Ci/mmol; Amersham International). Autoradiography was carried out using a Sakura NR-M2 emulsion, and after exposure for 7 days at 4°C, numbers of silver grains over nuclei in 30–50 cells were counted. The amount of UDS in XP cells was expressed as a percentage of that in normal cells which were assayed in parallel.

## RESULTS

**Clinical Features** The clinical data and the cellular characteristics of the three completely analyzed XP group E cases are given in Table I.

*Case 1* A 50-yr-old Japanese female (XP80TO) first noticed acute moderate sunburn without blistering at age 8–9 yr. At age 18 yr, pigmented macules appeared on her face and gradually increased in the number. At age 46 yr, she developed three basaliomas on the upper chest, right side of the nose and upper lip, and an actinic keratosis at the left outer angle of the eye. These neoplasms had been excised and histologically confirmed at another hospital. On her first visit at the age of 50 yr, she exhibited freckles on her face, neck, forearms, and legs. The skin showed slight dryness and xerosis. Her parents are second cousins. She said that her elder brother, 52 years old, also showed sun sensitivity and many freckles on the exposed skin areas. However, he has not yet been examined in detail.

*Case 2* A 42-yr old Japanese female (XP81TO) showed sun sensitivity with severe erythema and blistering at age 5 yr. At age 20 yr, she manifested freckles on sun exposed areas and palpebral conjunctivitis. At age 41 yr, she developed two small skin tumors, which

**Table I.** Clinical Data and Cellular Characteristics of Group E Patients

| Group E[a] Patient | Sex | Age | Parental Relationship | Age at Onset: UV-erythema | Age at Onset: Freckle | Age at Onset: Skin Malignancies | Abnormalities: P[b] | Abnormalities: D[c] | Abnormalities: N[d] | Skin Photo-Test: MED | Skin Photo-Test: Peak of Erythema | Mean UDS (% of normal cells): Fibroblasts | Mean UDS (% of normal cells): Keratinocytes | UV Killing: $n$ | UV Killing: $Do$ (J/m$^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XP24KO | F | 16 | — | 1 yr[e] | 11–12 yr | — | — | — | — | low | 24 h | 40 | | 1.5 | 2.3 |
| XP26KO | M | 8 | — | 1 yr | 5–6 yr | — | — | — | — | normal | 24 h | 35 | | 1.8 | 2.4 |
| XP70TO | F | 5 | — | 3–4 m[f] | 3 yr | — | — | — | — | low | 72 h | 55 | 77 | 1.2 | 2.2 |
| XP80TO | F | 50 | — | 8–9 yr | 18 yr | 46 yr BCE[g] (3)[h] | — | — | — | low | 48 h | 43 | 38 | 1.3 | 2.2 |
| XP81TO | F | 42 | — | 5 yr | 20 yr | 41 yr BCE (2) | — | — | — | low | 48 h | 40 | 38 | 1.4 | 2.5 |
| XP82TO | F | 40 | — | 5 yr | 6 yr | — | — | — | — | low | 24 h | 44 | 51 | 1.8 | 2.8 |
| XP2RO | F | 16 | second cousins | | | 14 yr Carcinoma | | | | | | 40[i] | | | |
| XP3RO | F | 29 | | | | — | | | | | | 45[i] | | | |
| XP34MA | F | 24 | sisters | | 6 yr | 16 yr BCE (5) | | | | | | 61[j] | | | |
| XP35MA | F | 33 | | | 9 yr | 17 yr BCE (3) | | | | | | 65[j] | | | |
| XP41MA | F | 20 | | | 9 yr | 20 yr BCE (2) | | | | | | 70[j] | | | |

[a] Patients XP24KO and XP28KO were reported by Fujiwara et al [7], patient XP70TO by Kawada et al [8], patients XP2RO and XP3RO by de Weerd-Kastelein et al [4] and Kraemer et al [7], and patients XP34MA, XP35MA, and XP41MA by Fischer et al [6]. KO, Kobe; TO, Tokyo; RO, Rotterdam; MA, Mannheim.
[b] P = Perinatal.
[c] D = Developmental.
[d] N = Neurological.
[e] y = years.
[f] m = months.
[g] BCE = Basal cell epithelioma.
[h] Numbers in parentheses indicate the number of tumors.
[i] UDS data from references 4, 7.
[j] UDS data from reference 6.

revealed histological characteristics of basalioma. On her first visit at age 42 yr, she manifested freckles on her face, upper chest, shoulders, upper extremities, and lower legs, and slight dryness of the exposed skin.

*Case 3* A 41-yr-old female Japanese (XP82TO) showed acute sun sensitivity reaction without blistering at age 5 yr; she also developed pigmentanomaly on the arms and thighs, as well as freckles on the face around age 6 yr. On her first visit, she exhibited pigmented and depigmented macules and patches on the face, neck, chest, and extremities, especially the dorsi of the hands. The exposed skin showed slight dryness and xerosis. Her elder brother was said to have many freckles, but no skin neoplasms. However, he has not yet been examined in detail.

The three patients described above were normal at birth and have shown normal development. They had neither substantial neuromental deteriorations (including hyporeflexia or areflexia of the tendons, sensorineural deafness audiometerically, clumsy gait, speech impairment, swallowing difficulties, and mental retardation) nor ophthalmological abnormalities (including photophobia, conjunctivitis, and keratitis), except for a cataract in XP80TO.

All these patients have been treated by sun protection, using Pre-Sun 15 ("Creamy") (Westwood Pharmaceutical Inc., USA) and crème écran total antisolaire (Roc S.A., France) for the skin, écran labial hydratant (Roc S.A., France) for the lips, and Nikon SX-13 UV-cut spectacles (Nippon Kogaku K.K., Japan) for the eyes. Patient XP80TO developed four additional small skin tumors (histologically actinic keratoses) on the face, 4 months after the first examination.

**Photosensitivity Test of the Skin** The skin erythema test on patients XP80TO and XP81TO showed a delayed maximum reaction at 48 h and lower minimal erythema doses (MEDs) of 9.4–12.6, 8.6–8.8, and 17.3–18.0 mJ/cm² at 280, 290, and 300 nm monochromatic wavelengths of UV light, respectively. Such values are within $-0.7 \sim -2.6$ SD of the 24 h MEDs at the maximum reaction of normal subjects ($16.4 \pm 5.2$, $17.6 \pm 3.7$, and $45.1 \pm 10.5$ mJ/cm² at 280, 290, and 300 nm, respectively), but apparently a little higher than those at 72 h in the group A patients (Fig 1). Patient XP82TO also showed lower MEDs of 11.3 and 27.4 mJ/cm² at 290 and 300 nm monochromatic UV light, respectively, but not the delayed peak reaction of skin erythema.

**Clonogenic UV Survival** Figure 2 shows the 254-nm UV survival curves of XP80TO, XP81TO, and XP82TO cells in comparison with those of NHSF6 normal cells and XP6KO group A cells. The three cell strains exhibited about the same, twofold higher UV sensitivity ($n = 1.2–1.8$, $Do = 2.2–2.8$ J/m²) as compared with NHSF6 cells ($n = 1.5$, $Do = 5.0$ J/m²), but showed less UV-sensitivity than did group A XP6KO cells ($n = 1.0$, $Do = 0.5$ J/m²), as described previously [11].

**Complementation Analysis and Measurement of Unscheduled DNA Synthesis** Figure 3 shows the complementation results. The XP80TO/XP24KO heterodikaryons showed nonnormalized UDS of about 43% of normal (NHSF6/NHSF6) homodikaryons, which was identical to the relative UDS of the XP80TO/XP80TO and XP24KO/XP24KO homodikaryons after irradiation with 10 J/m². Therefore, XP80TO cells were considered not to complement the reference group E XP24KO cells. In contrast, all of the heterodikaryons between XP80TO and the other reference XP strains revealed a normal level of UDS as high as 90%–100% as a result of positive genetic complementation, as did the NHSF6/NHSF6 homodikaryons and the XP80TO/NHSF6 heterodikaryons (Fig 3*A*). Consequently, XP80TO cells unable to complement only the reference XP24KO (E) cells were assigned to XP group E.

Figures 3*B* and 3*C* show the complementation results of XP81TO and XP82TO, respectively. The complementation patterns in the various dikaryons were very similar to those depicted in Fig 3*A* for XP80TO cells. Only the failure of both XP81TO and XP82TO cells in complementing the XP24KO reference group E cells in their heterodikaryons allowed us to assign them to group E.

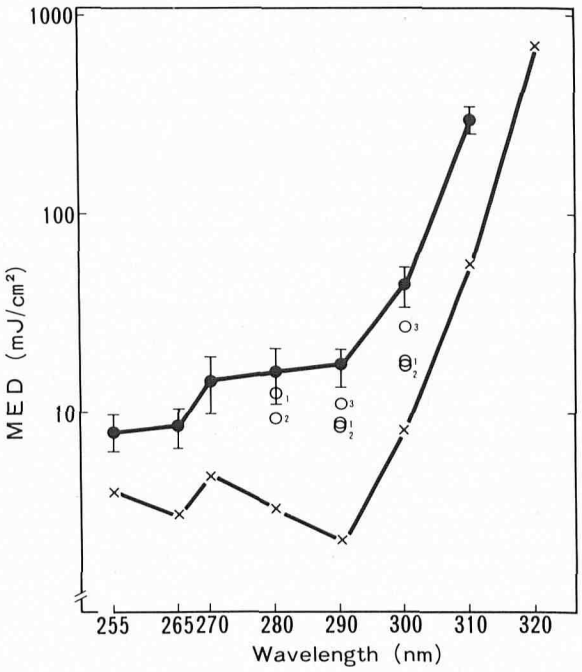


**Figure 1.** MEDs of XP80TO, XP81TO, and XP82TO. MEDs were measured by monochromatic UV light. $O_1$, MED of XP80TO measured 48 h after irradiation; $O_2$, MED of XP81TO measured 48 h after irradiation; $O_3$, MED of XP82TO measured 24 h after irradiation; *circle and bar,* mean MED and standard deviation of 74 normal Japanese subjects, measured 24 h after irradiation; *X*, mean MED of group A patients (21 cases, aged 1–13 yr), measured 72 h after irradiation.

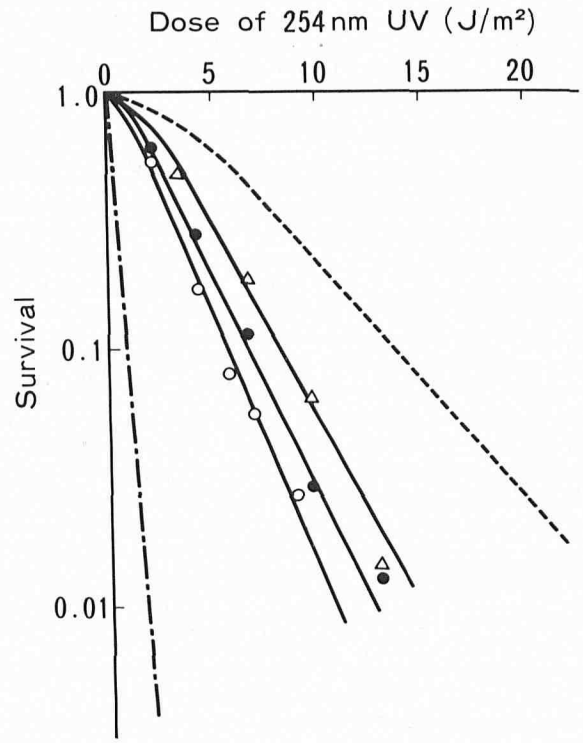


**Figure 2.** Clonogenic UV-survival cureves. Cells in log-growth phase were plated at appropriate numbers. After attachment, cells were washed with phosphate-buffered saline, irradiated with 254 nm UV light, and incubated for 2 wk to determine clone survival. The NHSF6 normal strain represents the average of UV survival curves of the 5 other normal strains. *Open circle,* XP80TO ($n = 1.3$, $Do = 2.2$ J/m²); *filled circles,* XP81TO ($n = 1.4$, $Do = 2.5$ J/m²); *open triangle,* XP82TO ($n = 1.8$, $Do = 2.8$ J/m²); *dashed line,* XP6KO (A) ($n = 1.0$, $Do = 0.5$ J/m²); *dotted line,* NHSF6 ($n = 1.5$, $Do = 5.0$ J/m²).

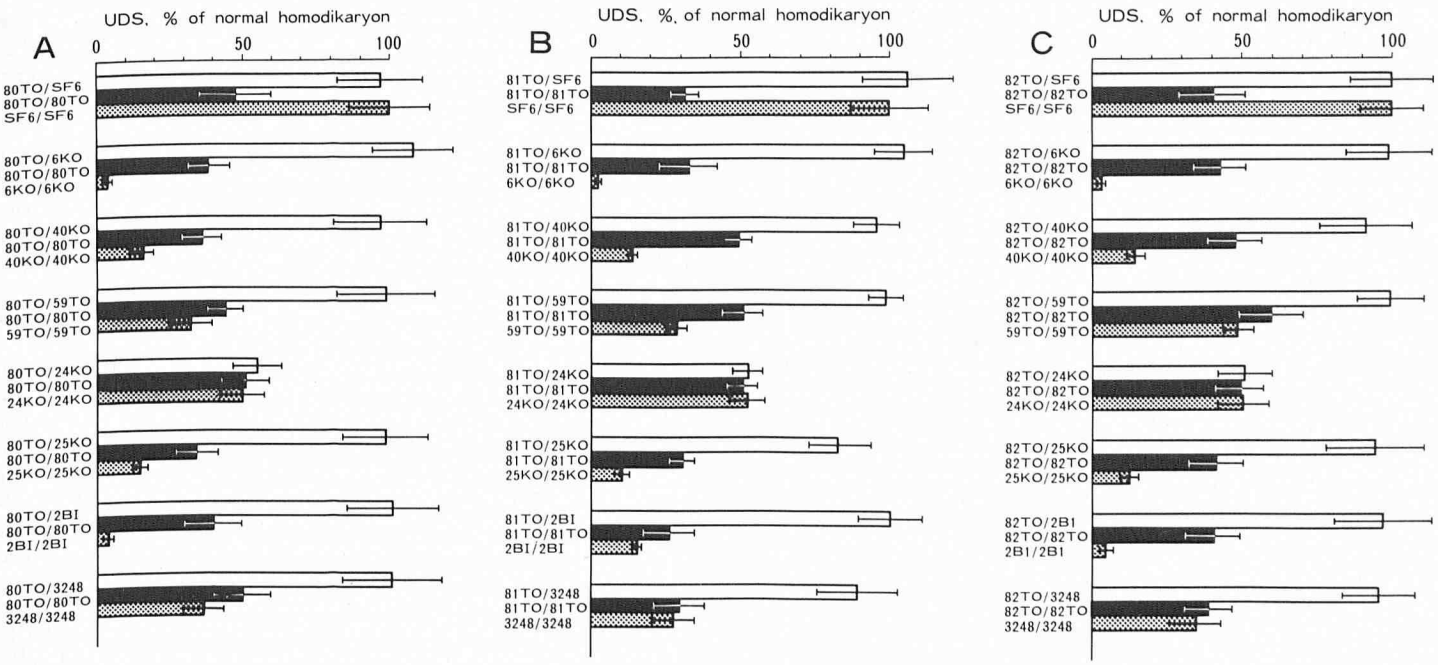


**Figure 3.** Genetic complementation by cell fusion. The test (XP80TO, XP81TO, and XP82TO) and reference [SF6 (normal, *N*), 6KO (A), 40KO (C), 59TO (D), 24KO (E), 25KO (F), 2BI (G), GM3248 (H)] cells were LB- and SB-labeled, respectively, cocultured at a high cell density, and hybridized with polyethylene glycol. Subsequently, sparse cultures on coverslips were incubated for 24 h, irradiated with 254-nm UV light (10 J/m$^2$), and labeled with [$^3$H]thymidine for 3 h, as described in the text. UDS was measured on heterodikaryons (LB/SB, *clear bars*) and homodikaryons (LB/LB for test cells, *solid bars;* SB/SB for reference cells, *shaded bars*), and expressed as percentages of normal (NHSF6/NHSF6) homodikaryons. *(A)* Complementation test for XP80TO; *(B)* Complementation test for XP81TO; *(C)* Complementation test for XP82TO. In these figures only, the prefixes of the strain names (XP, NH, and GM) were omitted. The *bar* of histogram indicates standard deviation.

Furthermore, the relative amounts of UDS were 40% and 44% for the XP81TO homodikaryons and the XP82TO homodikaryons, respectively.

In order to confirm the above assignments, we performed cross-hybridization in a separate experiment under the identical conditions. Table II shows the results which indicate that the relative amounts of UDS in the cross-hybridized heterodikaryons of XP80TO/XP81TO, XP80TO/XP82TO, and XP81TO/XP82TO remained at the same lower levels of 49%–51% of the control NHSF6/NHSF6 homodikaryon, indicating that no complementation occurs between either two of XP80TO, XP81TO, and XP82TO. Thus, the present three group E fibroblast strains have the very similar amount of lowered UDS, which falls in the previously reported range of 40%–60% UDS in group E.

**Ultraviolet-Induced Unscheduled DNA Synthesis in Primary Cultured Epidermal Cells** The mean grain numbers of the normal control cells were found to be within the normal range of the previous data [9] (ie, 29.4 ± 4.6 at 5 J/m$^2$, 42.3 ± 8.9 at 10 J/m$^2$ and 53.3 ± 11.8 at 20 J/m$^2$) (Fig 4). The mean grain numbers of the epidermal cells isolated from XP group E patients displayed dose-dependent induction by radiation at doses of 5–20 J/m$^2$ (Fig 4). The extent of UDS in these XP epidermal cells exhibited relatively low levels of residual DNA repair: XP80TO, 37%–38%; XP81TO, 35%–41%; and XP82TO, 44%–58%. These were similar to those in their respective fibroblasts (Table III). We also measured UDS in epidermal cells from group E XP70TO, which we reported previously [8]; the figure was 69%–84% of that in normal epidermal cells (Fig 4, Table III).

## DISCUSSION

We reported three female Japanese patients (XP80TO, XP81TO, and XP82TO) with mild clinical signs of XP, such as moderate sun sensitivity, pigmentation, and depigmentation in sun-exposed areas, and with late onset of skin malignancies. These patients were examined dermatologically, ophthalmologically, otorhinolaryogologically, and neurologically. The DNA repair capacity was measured by means of the post-UV colony-forming ability and UDS of their fibroblasts, and by measurement of UDS in primary cultured epidermal cells.

Worldwide, the incidence of group E patients is still rare. To our knowledge, only 11 cases, consisting of six cases (XP24KO,

**Table II.** Complementation Test for Cross-Hybridized Heterodikaryons between the Present Group E Strains

| Heterodikaryon | UDS | | Complementation |
|---|---|---|---|
| | Mean Grain Counts per Nucleus of Dikaryon | % of Normal Homodikaryon | |
| Normal homodikaryon | | | |
| NHSF6/NHSF6 | 73.05 ± 11.83[a] | 100 | |
| XP heterodikaryons | | | |
| XP80TO/NHSF6 | 72.31 ± 12.50 | 99 | + |
| XP80TO/XP81TO | 36.10 ± 4.31 | 49 | − |
| XP80TO/XP82TO | 35.73 ± 5.59 | 49 | − |
| XP81TO/XP82TO | 37.06 ± 5.64 | 51 | − |

[a] Mean ± SD for 100 cells, corrected for the background.

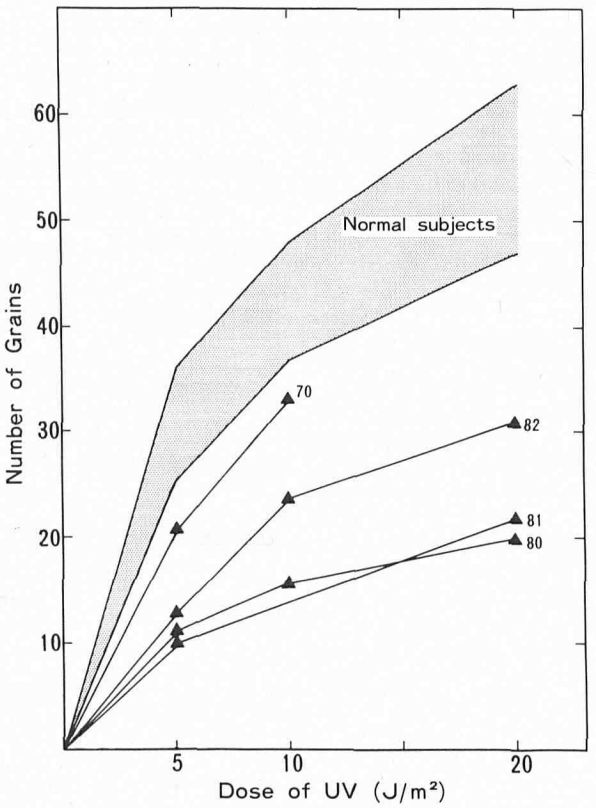


**Figure 4.** Dose-dependent induction of UDS by 254-nm UV radiation in normal and XP group E epidermal cells. The range of UDS in normal epidermal cells (26 normal subjects, aged 3 m–56 yr) is indicated by the *shaded area.* The *closed triangles* numbered by 70, 80, 81, and 82 represent XP70TO, XP80TO, XP81TO, and XP82TO, respectively.

XP26KO [7], and XP70TO [8] and the present XP80TO, XP81TO, and XP82TO) from Japan and five cases (XP2RO, XP3RO [4,5], XP34MA, XP35MA, and XP41MA [6]) from Europe, have been assigned to complementation group E.

The characteristics of these group E patients are summarized in Table I. All exhibited relatively late onset of the disease (except patient XP70TO), mild clinical symptoms, no observable neurologic, perinatal, and developmental abnormalities, lower MEDs (except patient XP26KO), and an intermediate UV hypersensitivity of fibroblasts ($n = 1.2-1.8$, $Do = 2.2-2.8$ J/m²). The group E patients in Europe had family relationships (XP2RO and XP3RO were second cousins, and XP34MA, XP35MA, and XP41MA were sisters), and all but one of them developed skin malignancies by age 20 yr, whereas those in Japan were unrelated and only two of six patients (XP80TO and XP81TO) developed skin malignancies around age 40 yr.

DNA repair in XP epidermal cells has been studied in the skin in vivo [18], in isolated epidermis in vitro [20,21], and in short-term cultures of trypsin-dissociated epidermal cells [19]. Those studies have shown that epidermal cells from repair-defective XP patients (groups not indicated) exhibit low levels of UV-induced UDS, more or less comparable with those in dermal fibroblasts, and XP variant epidermal cells show almost normal level of UDS [18–21]. We have demonstrated by use of explant-outgrowth cultures of epidermal cells that XP groups A, E, and variant show various degrees of lowered UDS [9]. By this culture method, Fig 4 and Table III have shown that epidermal cells from the 4 group E patients exhibit relatively low levels of UV-induced UDS, almost comparable with those induced in the fibroblastic cells: 38%–77% in epidermal cells versus 40%–55% in fibroblasts.

Satoh et al [3] and Takebe et al [22] investigated the incidence of various skin cancers in Japanese patients with XP in relation to DNA repair defects in their fibroblasts. They suggested that the lower the level of DNA repair in XP fibroblasts, the earlier and the more severe the XP symptoms and cancers develop. In the present study, we found that two of the four group E patients developed skin malignancies at the 4th decade of age, and that their epidermal cells and fibroblasts exhibited 38%–43% UV-induced UDS. These results are in accordance with the previous works [3,22]. However, there is still no precise understanding of the molecular defect(s) in DNA repair and carcinogenesis in XP. To clarify skin carcinogenesis, further studies, especially on epidermal cells, are certainly needed on patients belonging to group E, as well as the other complementation groups, because epidermal cells are a target for skin carcinogenesis. We wish to emphasize that mild forms of XP should not be overlooked and the cellular characteristics of such patients should be intensively examined.

**Table III.** UDS in XP Group E Epidermal and Dermal Cells

| Group E Patient | Mean UDS (% of normal cells) | |
|---|---|---|
| | Epidermal | Dermal |
| XP70TO | 77 (69–84)[a] | 55 (53–56) |
| XP80TO | 38 (37–38) | 43 (34–51) |
| XP81TO | 38 (35–41) | 40 (27–52) |
| XP82TO | 51 (44–58) | 44 (37–47) |

[a] Values in parentheses indicate the range of UDS on UV irradiation at 5 to 20 J/m².

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